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Background

The last 10 years have seen a remarkable increase in the understanding of the biology of numerous primary brain tumors. This is also reflected by the most recent edition of the World Health Organization (WHO) classification of tumors of the central nervous system (CNS) which was released in 2016. In the new WHO classification, CNS tumors are not only categorized based on histopathological features but for the first time also by additional molecular parameters [1]. Within the last decade, numerous high-throughput analyses, e.g. within the Cancer Genome Atlas (TCGA) project [2], have been performed for different brain tumor entities. It can be safely assumed that the current edition of the WHO classification represents only the first step towards a detailed molecular characterization of many brain tumors and already now a plethora of specific molecular alterations in different CNS tumors has been recognized which have not yet entered the WHO grading system. In this overview, we summarize some key findings on the molecular level in the most common primary brain tumors with a particular focus on those alterations that are helpful for diagnostic purposes and clinical decision-making.

Diffuse Gliomas

A cornerstone in the molecular subclassification of gliomas was the identification of mutations in the *isocitrate dehydrogenase* (IDH) 1 and 2 genes. Sequencing revealed that the majority of WHO grade II and approximately 60% of all WHO grade III gliomas harbor a mutation in either of the 2 genes [3]. In contrast, only a minority of glioblastomas displays an IDH mutation [4]. Because of their uniform presence across the tumor cell population in IDH mutation-positive tumors, IDH mutations are regarded as an early event during gliomagenesis. Across all WHO grades, IDH-mutated gliomas have a better prognosis than their counterparts with IDH wild-type genes with similar histology [5]. IDH-mutant tumors are now generally considered to represent different disease entities, potentially overruling histological appearance, and the role of WHO grading versus that of other molecular markers within the tumor groups defined by IDH mutation status needs to be reassessed.

According to the new WHO classification, a 1p/19q co-deletion, also referred to as *loss of heterozygosity* (LOH) 1p/19q, is mandatory to render the definite diagnosis of an oligodendroglial tumor. LOH 1p/19q is probably always associated with an IDH mutation. 1p/19q-codeleted tumors have a better prognosis than 1p/19q-intact gliomas and the predictive role of a 1p/19q co-deletion for benefit from polychemotherapy using procarbazine, vincristine and lomustine (PCV) has been shown repeatedly in WHO grade III grade tumors [6, 7] and more recently in WHO grade II tumors [8].

In addition to these two major diagnostic markers stressed in the new WHO classification, IDH and 1p/19q codeletion status, the methylation status of the promoter region of the O^6-methylguanine-DNA methyltransferase (MGMT) gene continues to impact clinical decision making in patients with diffuse gliomas of adulthood. MGMT confers resistance to alkylating agents such as temozolomide by removing treatment-induced DNA lesions [9]. It is now widely accepted that MGMT promoter methylation predicts benefit from alkylating agent chemotherapy in glioblastoma. There may also be a predictive role for MGMT in IDH wild-type lower-grade gliomas, but possibly not in IDH-mutated tumors [10]. Testing for MGMT status is done by methylation-specific PCR or by pyrosequencing. Since there is no alternative to temozolomide in the first-line setting and since temozolomide is commonly well tolerated, younger patients with newly diagnosed glioblastoma are still treated with a combination of radiotherapy and temozolomide chemotherapy independent of the MGMT promoter methylation status, although clinical trials with omission of temozolomide in the first-line setting for patients with tumors without MGMT promoter methylation are increasingly considered an option [11]. However, MGMT is a clinically useful marker for therapeutic decision making in elderly and frail patients who may not be eligible for combined modality treatment [12-14].

The comprehensive molecular profiling of gliomas has revealed many other biological alterations which are increasingly used for diagnostic purposes. This includes mutations in the promoter region of the gene encoding *telomerase reverse transcriptase* (TERT) as well as mutations in the *α-thalassemia/mental-retardation-syndrome-X-linked* (ATRX) gene which are frequently found in oligodendrogliomas and glioblastomas (TERT) respectively IDH-mutant astrocytic tumors (ATRX) [15, 16]. Furthermore,

the newly defined group of «diffuse midline gliomas» is characterized by mutations in the H3F3A gene [17].

Other gliomas

Pilocytic astrocytomas

Pilocytic astrocytomas are rare in adults but represent frequent CNS tumors in the pediatric population. Similar to diffuse gliomas, their molecular landscape has been described in detail. Pilocytic astrocytomas may be considered a single-pathway disease with virtually all tumors harboring alterations in the *mitogen-activated protein kin*ase (MAPK) pathway [18]. The most frequent finding is a fusion between the *KIAA1549* gene and the *BRAF* oncogene but there are also other mechanisms resulting in a MAPK activation. Targeting the activated pathway, e.g. by *mitogen-activated protein kinase kinases* (MEK) inhibitors, is currently explored as a novel therapeutic approach in clinical trials.

Gangliogliomas and pleomorphic xanthoastrocytomas

BRAF mutations have been described in a subgroup of gangliogliomas and xanthoastrocytomas. Similar to pilocytic astrocytomas, molecular testing for the activating BRAF mutation V600E is warranted in patients with progressive tumors that are no longer eligible for surgery or radiation therapy. Several case reports and retrospective series suggest that BRAF inhibition with vemurafenib or dabrafenib may result in clinically relevant anti-tumor activity [19].

Ependymomas

Ependymomas have been reclassified based on three different localization patterns in the CNS: supratentorial, posterior fossa and spinal, as well as based on DNA methylation profiling, resulting in 9 subgroups of ependymal tumors [20]. The 2016 WHO classification has only partially incorporated these novel findings. The presence of an oncogenic fusion between *RELA* and *C11orf95* indicates a supratentorial tumor with poor prognosis that is more frequent in children than in adults. Similar to other brain tumors, it can be expected that the detailed genetic profiling of ependymomas will result in a further segregation of these tumors into specific subgroups.

Subependymal giant cell astrocytomas

Subependymal giant cell astrocytomas (SEGA) are typically found in patients affected by tuberous sclerosis complex (TSC). This disease is characterized by a dysregulation of the mammalian target of rapamycin (mTOR) pathway because of an alteration in the *TSC1* or *TSC2* gene. mTOR inhibition using drugs such as everolimus has emerged as a powerful therapeutic approach that results in a reduction of SEGA volume and sustained growth inhibition in the majority of patients [21].

Meningiomas

Meningiomas account for approximately 35% of all primary brain tumors. They are mostly benign tumors that can be cured by surgical resection. However, some of these tumors display histological features of malignancy and also meningiomas categorized as WHO grade I tumors may recur and rarely cause distant metastasis. In the last few years, several reports have described a set of gene mutations that are frequently found in meningiomas including mutations in *AKT1*, *SMO*, *TRAF7*, *KLF4* and *PIK3CA* [22-24]. Some of these mutations correlate with histological subtypes and tumor localization in the brain [25]. So far, testing for these molecular alterations is not yet part of the standard diagnostic. However, since mutations in the *AKT1* or *SMO* gene may be *actionable*, genetic testing should be considered in patients who have run out of standard treatment options. It needs to be awaited whether the first successful reports on targeted therapy for patients with progressive meningioma [26] can be translated into standard treatment options in the future.

Craniopharyngiomas

The genetic profiling of craniopharyngiomas has identified distinct molecular alterations that are associated with the well-known histophathological subgroups. Adamantinomatous craniopharyngiomas typically harbor a mutation of the beta-catenin gene (CTNNB1). Papillary craniopharyngiomas do not display this mutation but virtually all have a $BRAF^{V600E}$ mutation [27]. The latter may represent a novel therapeutic target and clinical trials exploring the activity of BRAF inhibitors are ongoing.

Medulloblastomas

Medulloblastoma is typically located in the cerebellum and more frequently diagnosed in children than in adults. The molecular characterization of these tumors has resulted in 4 different subgroups based on activations in the wingless (WNT) or sonic hedgehog (SHH) pathway as well as the groups 3 and 4 [28]. Medulloblastomas with an alteration in the WNT pathway have the best prognosis [29]. In the SHH subgroup, mutations in the p53 gene are associated with a particularly poor prognosis. Beyond its prognostic role, the molecular profiling may also be increasingly used for therapeutic decision-making. SHH-activated tumors may be sensitive to SMO inhibitors which may be used as an experimental treatment strategy in patients who have no further established treatment options.

Summary and outlook

High-throughput studies have paved the road for a detailed understanding of the molecular landscape of many brain tumors. Currently, only a small proportion of detectable molecular alterations is clinically relevant for diagnostic and therapeutic purposes. Assessing the IDH and 1p/19q status is mandatory to render the diagnosis of an astrocytic or oligodendroglial tumor. Similarly, testing for the presence of a KIAA1549:BRAF fusion or H3F3A

mutation allows for increased diagnostic accuracy in some patients. The MGMT promoter methylation status can be used for clinical decision-making, particularly in patients with IDH wild-type tumors who are not eligible for combined modality treatment. Although in-depth molecular characterization of brain tumors is feasible within a reasonable time and exhibits profound diagnostic power [30], the number of actionable molecular alterations with an impact on therapeutic decisions is still limited. However, not only in gliomas but also other brain tumors such as meningiomas and medulloblastomas, further developments in the molecular characterization of these neoplasms as well as the emergence of novel drugs will result in more personalized and patient-tailored treatment approaches in the next years.

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